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Simple and efficient deprotection of 1,3-dithianes and 1,3-dithiolanes by copper(II) salts under solvent-free conditions

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Abstract—Aerobic solid state deprotection of 1,3-dithianes and 1,3-dithiolanes of aromatic and aliphatic aldehydes and ketones has been performed in excellent yields by $Cu(NO_3)_2{\cdot}2.5H_2O$ in the presence of montmorillonite K10 clay and sonic waves at room temperature. These dethioacetalizations proceed more slowly but efficiently under catalytic conditions by using 20% of the copper(II) salt with K10 clay and sonication.

The protection of a carbonyl group is often a necessary step in organic synthesis, especially in the total synthesis of natural products and multifunctional organic compounds. Thioacetals and cyclic thioacetals (1,3-dithianes and 1,3-dithiolanes) are protecting groups commonly used due to their easy access and high stability under both acidic and basic conditions.[1] Furthermore, cyclic thioacetals are versatile synthetic reagents as acyl anion equivalents for C–C bond formation;[2] which is a common and successful strategy for the construction of complex natural products.[3]

Many procedures are available for the preparation of thioacetal; dethioacetalization, however, is not always an easy step.[1] Traditionally, deprotection of thioacetals[4] has required drastic conditions, stoichiometric or an excess amount of toxic reactives such as Hg^{2+} salts and other heavy metal salts from Bi^{3+}, Zn^{2+}, Zr^{2+}, V^{5+}, Ce^{3+}, Ta^{5+}, $SbCl_5$[5] or SeO_2. In addition, there are methods under heterogeneous conditions which use montmorillonite K10 supported $Fe(NO_3)_3$ and $Cu(NO_3)_2$ (Clayfen and Claycop, respectively),[6] or NH_4NO_3 (Clayan);[7] $Cu(NO_3)_2$ supported on silica gel,[8] $Fe(NO_3)_3$/K10/hexane.[9] $FeCl_3{\cdot}6H_2O$,[10] $Fe(phen)_3(PF_6)_3$,[11] and other recent non-metallic reagents[12] have also been used in solution. Nevertheless, these methods have some disadvantages such as long reaction times, strong acids, toxic reagents and solvents, expensive catalysts or not readily available reactives, and unwanted side reactions.

Recently, an increased interest has been observed in reactions under solvent-free conditions to reduce contamination, lower costs, and simplify the process.[13] These procedures usually combine supported reagents and microwave[14] (MW) or ultrasonic irradiation[15] to carry out a wide range of reactions in shorter times and with high conversion and selectivity. Few examples of solid state dethioacetalization have been reported to use Clayfen/MW,[16] ammonium persulfate on wet K10 under MW,[17] $Fe(NO_3)_3{\cdot}9H_2O/H_3PMo_{12}O_{40}{\cdot}xH_2O$,[18] acidic ionic liquid [bmim]HSO_4/MW,[19] mercury(II) nitrate trihydrate[20] and benzyltriphenylphosphonium peroxymonosulfate[21] in the presence of $AlCl_3$.

Therefore, it is still necessary to develop alternative milder methods for dethioacetalization using inexpensive, not toxic and accessible reagents. Thus, we report herein a simple and convenient aerobic solvent-free deprotection of thioketals/thioacetals by copper(II) salts in the presence of montmorillonite K10 clay under ultrasonic irradiation (Scheme 1).

We have selected 2-phenyl-1,3-dithiolane (**1a**) as a model compound to examine the deprotection reaction by copper(II) salts under a variety of reaction conditions.

Keywords: Thioacetals; Solid state synthesis; Copper(II) salts; Oxidation; Cleavage; Ultrasound.

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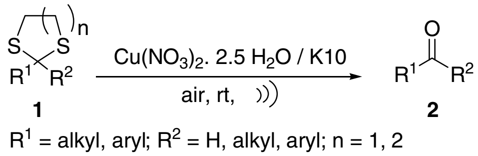
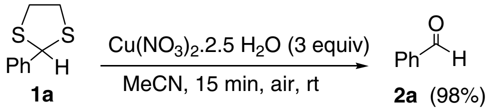


Scheme 1.

Before studying the solvent-free reaction, a comparative deprotection was performed in solvent media. Thus, the reaction of **1a** with $Cu(NO_3)_2{\cdot}2.5H_2O$ (1 equiv) in MeCN at rt in an open-air vessel afforded 92% of benzaldehyde after 180 min of stirring. With an excess of the Cu(II) salt (3 equiv) the reaction is quantitative after 15 min of stirring (Eq. 1). In CH_2Cl_2 this reaction was slower and was completed after 135 min. Comparable results were obtained under nitrogen atmosphere, indicating that in solution the presence of molecular oxygen is not necessary. The different reactivity observed in both solvents can be ascribed to a higher solubility of the copper salt in MeCN. In comparison, the dethioacetalization reported by Claycop (2 equiv) under heterogeneous conditions which employs a large excess of CH_2Cl_2 requires 5 h for a complete conversion.[6]



(1)

A series of conditions were found to affect the solvent-free deprotection reaction by Cu(II) salts with the results illustrated in Table 1. The deprotection of **1a** was explored using a solid state mixture of both $Cu(NO_3)_2{\cdot}2.5H_2O$ and montmorillonite K10.[22] In the absence of sonic waves only 1% yield of benzaldehyde was achieved after 3 h at room temperature, whereas ultrasonic irradiation enhanced the deprotection reaction rate and dethioacetalization of **1a** was completed after 2 h of sonication. Without the solid support K10, an equimolar solid mixture of **1a** and $Cu(NO_3)_2{\cdot}2.5H_2O$ afforded benzaldehyde in 92% yield after 3 h under sonic wave irradiation. The small amount of salt employed did not allow an efficient contact between both reagents and, due to a poor homogenization of the reaction system, the reaction was slower and consequently difficult to be reproduced (Table 1, entries 1–3). There was no reaction in the absence of $Cu(NO_3)_2{\cdot}2.5H_2O$, or in the presence of NH_4NO_3[23] or $CuSO_4$, and dithiane **1a** was recovered in 93–98% yields (Table 1, entries 4–6). The acetate salt was also non reactive and the bromide gave only 44% of benzaldehyde after 3 h of sonication (Table 1, entries 7 and 8). Thus, coordinating ligands decrease or eliminate catalytic activity in Cu(II) salts, specifically SO_4^{2-} or OAc^-.[24] A catalytic amount of HCl accelerates the reaction by $Cu(NO_3)_2$, even though its sole presence does not cause deprotection (Table 1, entries 9 and 10). These results clearly show that the nature of the ligand in the copper salt is essential, being the nitrate and, to a lesser extent, the bromide, only reactive for the dethioacetalization. K10 clay behaves only as an acidic support to favor the homogenization of both reagents. When washed sand was used instead of K10, a complete deprotection was also obtained. Finally, when the reaction was performed under nitrogen atmosphere, only a 7% yield of benzaldehyde was quantified. This indicates that the presence of air is required for a complete deprotection of the dithiane by the copper salt (Table 1, entry 11).

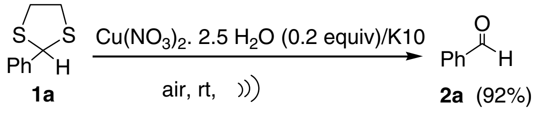
Table 1. Solvent-free deprotection of thioacetal **1a** by copper(II) salts[a]

Entry	Conditions	Time (min)	Product yield[b] (%)
1[c]	$Cu(NO_3)_2{\cdot}2.5H_2O$/K10/air	180	1
2	$Cu(NO_3)_2{\cdot}2.5H_2O$/K10/air	120	94
3	$Cu(NO_3)_2{\cdot}2.5H_2O$/air	180	92
4	K10/air	180	0[d]
5	NH_4NO_3/K10/air	180	0[d]
6	$CuSO_4$/K10/air	180	0[d]
7[e]	$Cu(OAc)_2$/K10/air	180	0[f]
8	$CuBr_2$/K10/air	180	44[g]
9	$Cu(NO_3)_2{\cdot}2.5H_2O$/K10/air/HCl (0.6 equiv)	25	92
10	HCl (0.6 equiv)/air	180	0[d]
11	$Cu(NO_3)_2{\cdot}2.5H_2O$/K10/N_2	180	7[d]

[a] All reactions run at room temperature, with 1 mmol of **1a** and 1 mmol of the inorganic salt and/or 1.3 g of K10, under sonication.
[b] Isolated yield.
[c] In the absence of sonic waves.
[d] 93–98% of unreacted **1a** was recovered.
[e] Dithiane of 4-cyanobenzaldehyde (**1b**).
[f] 98% of unreacted **1b** was recovered.
[g] 54% of unreacted **1a** was recovered.

A variety of 1,3-dithianes and 1,3-dithiolanes of aromatic and aliphatic aldehydes and ketones were subject to the optimized deprotection conditions (Table 1, entry 2) as described in Table 2. This method provides a general and benign removal of thioacetals and thioketals on substrates which bear different functional groups, including electron acceptor and electron donor groups. Thioacetals are more reactive than thioketals, and the presence of EWG on the phenyl ring apparently accelerates the reaction in comparison with electron donor groups (Table 2, entries 8 and 9). Furthermore, a higher reactivity is observed for 1,3-dithiane derivatives in relation to the corresponding 1,3-dithiolanes.

For environmental reasons, it is fundamental to reduce the use of copper salts under catalytic conditions. Therefore, only 0.2 equiv of $Cu(NO_3)_2$ was employed to perform the cleavage of thiolane **1a** (Eq. 2).[25]

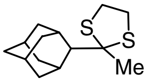
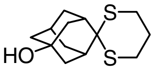


(2)

As illustrated in Table 3, very good to excellent deprotection is achieved by these mild conditions; the general process is slowed down providing a major selectivity. Thus, the ketone derivatives are markedly less reactive than the aldehyde derivatives, probably as a result of steric hindrance in the oxidation pathway.

To gain insight into the reaction mechanism we examined the possibility of a one-electron oxidation pathway

Table 2. Deprotection of 1,3-dithiolanes/1,3-dithianes (**1**) with $Cu(NO_3)_2{\cdot}2.5H_2O$/K10 under solvent-free conditions[a]

Entry	Substrate				Time (h)	Yield[b] (%)
	n		R^1	R^2		
1	1	**1a**	Ph	H	3	98
2	1	**1b**	p-NCC_6H_4	H	1.5	97[c]
3	1	**1c**	Ph	Me	5.5	84
4	1	**1d**	Ph	Ph	3.5	98[c]
5	1	**1e**	R^1–R^2 = –$(CH_2)_5$–		4.5	92
6	1	**1f**			11	90
7	2	**1g**	Ph	H	2.5	99
8	2	**1h**	p-NCC_6H_4	H	0.8	99[c]
9	2	**1i**	p-$MeOC_6H_4$	H	2	95
10	2	**1j**	Ph	Me	4	93
11	2	**1k**	Ph	Ph	2	93[c]
12	2	**1l**	Et	Me	1	93
13	2	**1m**			6	95

[a] All reactions run at room temperature, with 1 mmol of **1** and 1 mmol of the inorganic salt and 1.3 g of K10, under sonication.

[b] Isolated yield by extraction with *n*-hexane.

[c] Isolated yield by extraction with CH_2Cl_2.

for this dethioacetalization. $Cu(OAc)_2$ and $Cu(OTf)_2$ salts are one-electron oxidants for the generation of radical from lithium enolates and silyl enolether, respectively.[26] Aliphatic and aromatic dithianes and dithiolanes have oxidation potentials typically between 1.0–1.6 V (vs SCE).[27] Since trisphenanthroline iron(III) hexafluorophosphate, ($E_{1/2} = 0.69$ V) has proved to be a one-electron oxidant able to deprotect 1,3-dithianes in solution,[11] an ET oxidation of dithiane or dithiolane by Cu(II) is also likely to be a favorable process ($Cu(OTf)_2$, $E_{1/2} = 0.67$ V).[28] The ability of $Cu(NO_3)_2$ to oxidize sulfur compounds by an ET pathway was assessed by means of cinammyl phenyl sulfide (**3**) as a model compound to test the intermediacy of sulfur-centered radical cation. It is known that $\mathbf{3}^{\cdot+}$ affords the thiyl radical and the stabilized cinnamyl cation by fragmentation of the C–S bond. These intermediates finally render the disulfide and cinnamyl alcohol. Further oxidation of alcohol **4** yields cinnamaldehyde and benzaldehyde, the latter by oxidative cleavage of the double bond (Scheme 2).[29]

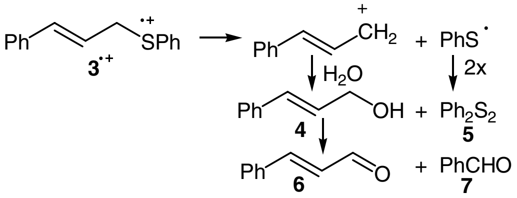
Table 3. Catalytic deprotection of 1,3-dithiolanes/1,3-dithianes (**1**) with $Cu(NO_3)_2{\cdot}2.5H_2O$/K10 under solvent-free conditions[a]

Entry	Substrate	Time (h)	Yield[b] (%)
1	**1a**	4.5	92[c]
2	**1b**	2.5	98
3	**1d**	24	91
4	**1h**	4	96
5	**1k**	24	95
6	**1e**	48	80

[a] All reactions run at room temperature, with a ratio substrate: $Cu(NO_3)_2{\cdot}2.5H_2O$ of 1.0:0.2 and 0.6 g of K10, at room temperature under sonication.

[b] Isolated yield by extraction with CH_2Cl_2.

[c] Isolated yield by extraction with *n*-hexane.

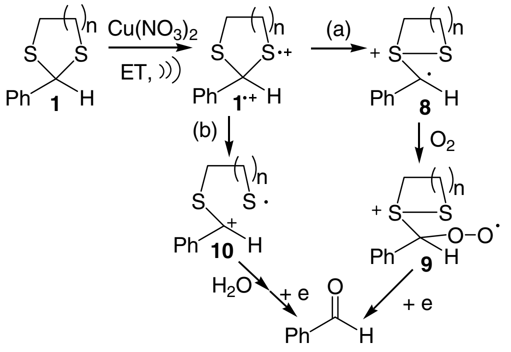


Scheme 2.

The aerobic oxidation of sulfide **3** by the Cu(II) salt in solid state rendered the fragmentation products **5**, **6**, and **7** after 4 h under sonication (Eq. 3).[30] This reaction was strongly inhibited by the presence of a good electron donor such as 1,2,4,5-tetramethoxybenzene[31] (TMB, 1 equiv), and 91% of the sulfide **3** was recovered after sonication.

$$\mathbf{3} \xrightarrow[\text{4h, air, r.t.)))}]{Cu(NO_3)_2.\ 2.5\ H_2O\ /\ K10} \underset{(28\%)}{\mathbf{5}} + \underset{(30\%)}{\mathbf{6}} + \underset{(38\%)}{\mathbf{7}} \qquad (3)$$

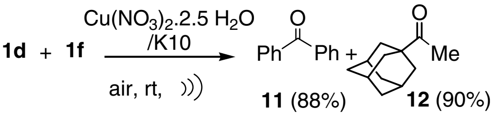
A similar result was observed when the deprotection reaction of **1a** was performed in the presence of the TMB (1 equiv) and 93% of **1a** was recovered after 2 h under sonic wave irradiation. When **1b** (1 mmol) was treated with a different amount of $Cu(NO_3)_2$ (1 mmol, 0.2 mmol and 0.1 mmol), conversion to **2b** was completed after 1.5 h, 2 h and 3.5 h of sonication, respectively. This suggests a catalytic cycle for the dethioacetalization. The strong inhibition by a better electron donor found, and the fragmentation products observed in the reaction of **3**, evidence an ET process followed by fragmentation of the sulfur-centered radical cation in the deprotection reaction by $Cu(NO_3)_2$. A plausible mechanism is outlined in Scheme 3.[32] After ET, the sulfur radical cation can follow two competitive pathways: (a) C–S bond fragmentation to render the carbon radical **8**; this radical can be captured by



Scheme 3.

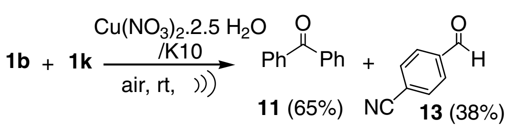
molecular oxygen to give the peroxy radical **9**, which rearranges to the carbonyl compounds through another ET step. (b) C–S bond fragmentation to afford a thiyl radical and the carbocation **10**; this cation can be attacked by water and finally converted to the carbonyl compounds.[33] The observation of dethioacetalization only in the presence of molecular oxygen in the solid state conditions, suggests the participation of pathway (a) for the formation of the carbonyl compound.[34] In contrast, the dethioacetalization reaction in homogeneous solution was not sensible to the atmosphere. This can be more adequately attributed to the occurrence of both competitive pathways, (a) and (b), Scheme 3.[35]

In general, the lower reactivity observed for 1,3-dithiolanes compared with 1,3-dithianes (for example, entries 2 and 8, Table 2) is in agreement with the oxidation potential 300–400 mV more positive than the corresponding dithiane. On the other hand, **1f** requires longer times of deprotection than **1d**. This cannot be ascribed to a less efficient ET process, since both substrates should have similar oxidation potential. Instead, the C–S bond fragmentation step and the subsequent ET pathways can be responsible for the difference in the global reactivity. Thus, for $\mathbf{1d}^{\cdot+}$ the C–S bond cleavage is faster since it renders a more stable diphenylmethyl radical. When an equimolar mixture of **1d** and **1f** was treated with 1 equiv of $Cu(NO_3)_2$/K10 under sonication for 3.5 h, and the resulting reaction mixture was extracted by *n*-hexane, benzophenone (**11**) and 1-adamantylmethylketone (**12**) were isolated in 88% and 90% yields, respectively (Eq. 4). An equilibration of both radical cations followed by a fast C–S bond fragmentation for $\mathbf{1d}^{\cdot+}$ triggers a faster dethioacetalization for both dithiolanes.



(4)

As previously mentioned, the presence of a more reactive thio-derivative in the propagation cycle accelerates the deprotection reaction of a less reactive sulfur compound (Eq. 4). The deprotection of **1d** or **1k** under catalytic conditions is expected to be faster in the presence of **1b** or **1h**. Therefore, an equimolar mixture of **1b** and **1k** was treated with $Cu(NO_3)_2$ (0.4 equiv) in the presence of K10 under sonication. After 2.5 h under sonic wave irradiation, the reaction mixture was extracted with *n*-hexane affording benzophenone (**11**) and 4-cyanobenzaldehyde (**13**) in 65% and 38% yields, respectively (Eq. 5). This example clearly shows the difference in reactivity for both compounds at the initiation (oxidative ET process) and propagation cycle. Seemingly, the C–S bond cleavage would govern the reactivity observed.



(5)

In conclusion, we have developed a very simple and efficient method for deprotection of dithianes and dithiolanes, which involves the use of a catalytic amount of $Cu(NO_3)_2$ under air atmosphere, sonication and solvent-free conditions. This protocol is a valuable alternative to the existing deprotection methods for economical and environmental reasons. Finally, the participation of the $Cu(NO_3)_2$ as one-electron oxidant was established. To the best of our knowledge this is the first report of oxidation of sulfur compounds by Cu(II) salts involving an ET process.

Representative experimental procedure for the general solvent-free deprotection: approximately 1.3 g of K10 was placed in an Erlenmeyer (50 mL). After the addition of $Cu(NO_3)_2 \cdot 2.5H_2O$ (1 mmol) and thioacetal (1 mmol), the reaction mixture was then lowered into a sonication bath (Ultrasonik 28X, 45–49 kHz) and sonicated at room temperature for the time specified in Table 2, which was optimized to achieve a complete conversion. After sonication, the mixture was washed with *n*-hexane, filtered, and the extract was analyzed by GC and GC–MS. Evaporation of the solvent under reduced pressure afforded the crude product that was purified by radial thin layer chromatography. The identity of all the products was confirmed by ^1H and ^{13}C NMR and MS spectrometry. The data for known compounds are in good agreement with those reported. Spectroscopic data for **1m** are provided.[36]

Acknowledgments

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28. Schmittel, M.; Langels, A. *J. Org. Chem.* **1998**, *63*, 7328–7337. All potentials are referenced versus the ferrocene/ferrocenium couple ($E_{1/2} = 0.39$ V vs. SCE) (Refs. 11 and 28).
29. Peñéñory, A. B.; Puiatti, M.; Argüello, J. E. *Eur. J. Org. Chem.* **2005**, 122–144.
30. The deprotection of the 1,3-dithiolane derivative from the cinnamaldehyde affords a mixture of cinnamaldehyde and benzaldehyde. The oxidative cleavage of the cinnamaldehyde by Cu(II) was not avoided even at shorter reaction times.
31. Ep^{ox} (TMB) = 0.77 V, versus SCE in MeCN (Ref. 5).
32. The absence of reaction in the presence of NH_4NO_3/K10 only, and the reactivity observed by $CuBr_2$ in our experimental conditions allow us to attribute the formation of the sulfide radical cation to a reaction with the Cu(II) ion. Nevertheless, a co-oxidation by NO_2 could not be entirely disregarded due to the formation of NO_2 (brown gas) observed at the end of the reaction. Bosch and Kochi reported that NO_2 can catalyze the O_2 oxidation of sulfides via the formation of an electron donor–acceptor (EDA) complex $[\text{sulfide},NO^+]NO_3^-$, followed by ET to produce a sulfur radical cation. Bosch, E.; Kochi, J. *J. Org. Chem.* **1995**, *60*, 3172–3183, Further electrochemical studies are required to elucidate the role of nitrate.
33. Pathway (a) has been proposed for the PET deprotection of dithiane by pyrilium salts under O_2 atmosphere Kamata, M.; Kato, Y.; Hasegawa, E. *Tetrahedron Lett.* **1991**, *32*, 4349-4352; whereas pathway (b) has been suggested for the dethioacetalization induced by visible light and dyes (Epling, G. A.; Wang, Q. *Tetrahedron Lett.* **1992**, *33*, 5909–5912) and indirect electrochemical oxidation, (Platen, M.; Steckhan, E. *Tetrahedron Lett.* **1980**, *21*, 511–514).
34. Another possibility would be a fast interconversion between the two distonic radical cations **10** and **8**, the former a carbocation with a thiyl radical, and the latter a carbon radical with a sulfur cation moiety.
35. The deprotection of dithianes with $Fe(phen)_3(PF_6)$ complexes and $SbCl_5$ requires an excess of the oxidant. Thus, the mechanism proposed to account for this dethioacetalization involves one-electron oxidation of a sulfur radical to a sulfonium ion as a key step. This intermediate by a second oxidative ET process affords a dication responsible for the formation of the ketone. Refs. 11 and 5.
36. Spectral data for 1,3-dithiolane **1m**: white solid. Mp 144.5–145.4°C, (petroleum ether). ^1H NMR (200 MHz, $CDCl_3$, 30 °C): $\delta = 1.44–1.51$ (m, 3H), 1.59 (d, 2H), 1.71 (s, 2H), 1.92–1.95 (m, 2H), 2.13 (s, 1H), 2.40–2.51 (m, 6H), 2.79–2.83 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$, 30 °C): $\delta = 25.1, 25.7, 26.0, 29.9, 31.4, 38.3, 40.3, 48.0, 57.5, 67.7$.